## Phylogeny

Tyrosine-protein kinase BLK is a subfamily-B member of the Src family of non-receptor tyrosine kinases. Orthologues are conserved throughout vertebrates and expression is essentially restricted to B lymphocytes. Phylogenetic analyses place BLK closest to the B-cell Src kinases Lyn and Fyn (Korade-Mirnics & Corey, 2000; Barreiro, 2017).

## Reaction Catalyzed

ATP + [protein]-tyrosine → ADP + [protein]-phosphotyrosine + H⁺ (Bolen & Brugge, 1997; Corey & Anderson, 1999).

## Cofactor Requirements

Catalytic activity requires divalent Mg²⁺ ions (Ingley, 2008; Bolen & Brugge, 1997).

## Substrate Specificity

BLK phosphorylates immunoreceptor activation motif (ITAM) substrates, notably CD79A (Y188, Y199) and CD79B (Y196, Y207), as well as Fcγ-receptor subunits FCGR2A, FCGR2B and FCGR2C. It also promotes Bruton’s tyrosine kinase (BTK) auto-phosphorylation. Substrates share acidic ITAM environments typical of Src-family targets (Barreiro, 2017; Bolen & Brugge, 1997; Corey & Anderson, 1999).

## Structure

BLK exhibits the canonical Src-family layout:  
• N-terminal SH4 domain, myristoylated/palmitoylated for membrane anchoring.  
• Unique region conferring isoform-specific regulation.  
• SH3 domain; an Ala71Thr variant heightens ubiquitination without altering localisation.  
• SH2 domain adjoining the catalytic (protein kinase) domain.  
• Short C-terminal tail containing an inhibitory tyrosine phosphorylated by Csk.  
(Korade-Mirnics & Corey, 2000; Barreiro, 2017; Bolen & Brugge, 1997; Superti-Furga & Courtneidge, 1995).

## Regulation

Activity is controlled by (i) phosphorylation of the activation loop (activating) and of the C-terminal tyrosine by Csk (inhibitory) and (ii) ubiquitin-mediated turnover, which is enhanced by the Ala71Thr SH3-domain variant via E6AP-dependent polyubiquitination (Barreiro, 2017; Bolen & Brugge, 1997; Korade-Mirnics & Corey, 2000; Mahajan et al., 1995).

## Function

Highly expressed in B lymphocytes, BLK initiates B-cell-receptor and pre-BCR signalling by phosphorylating CD79A/B, thereby triggering NF-κB activation and supporting the pro-B → pre-B transition (Barreiro, 2017). It facilitates BTK activation and interacts with the adaptor BANK1 (Barreiro, 2017). Additional reported roles include regulation of pancreatic β-cell transcription factors PDX1 and NKX6-1 (PubMed:19667185) and phosphorylation-dependent cytosolic retention of CGAS (PubMed:30356214).

## Inhibitors

Broad-spectrum Src-family inhibitors—dasatinib, ponatinib and saracatinib—bind the ATP pocket or allosteric sites and inhibit BLK (Sumera et al., 2023).

## Other Comments

Genome-wide association studies link reduced BLK expression to systemic lupus erythematosus and rheumatoid arthritis; BLK’s B-cell-restricted expression also suggests relevance to B-cell malignancies, although Src-family redundancy can compensate in knockout models (Barreiro, 2017; Bolen & Brugge, 1997; Korade-Mirnics & Corey, 2000).

## 9. References

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